Exhibit C

U.S. FOOD & DRUG ADMINISTRATION

Date: August 8, 2018

Zhejiang Huahai Pharmaceutical Co., Ltd.
Coastal Industrial Zone
Chuannan No. 1 Branch
Linhai, Zhejiang Province 317016

FEI: 3003885745

Subject: Amended Form FDA 483, Inspectional Observations

To: Mr. Jun Du, Executive Vice President

Enclosed please find an amended Form FDA 483, Inspectional Observations. Form FDA 483, Inspectional Observations, has been amended for the following corrections:
1. The firm address was corrected.
2. Added Joel Hustedt, Investigator to the Employee name block

Cheryl A. Clausen -S

Digitally signed by Cheryl A. Clausen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001563195, cn=Cheryl A. Clausen -S
Date: 2018.08.08 15:42:41 -04'00'

Cheryl Clausen, Investigator

U.S. Food and Drug Administration
Pharmaceutical Division II, Tampa-RP
3550 Buschwood Park Drive, Suite 230
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE Linhai, Zhejiang Province 317016 China	TYPE OF ESTABLISHMENT INSPECTED manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

QUALITY SYSTEM
OBSERVATION 1

The change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate. Specifically,

a) you do not always conduct a formal risk assessment for critical changes to evaluate the potential impact of proposed changes on the quality of intermediates or APIs. Critical Change Request PCRC-11025 was initiated November 27, 2011 and closed November 29, 2011, for the stated purpose of making changes to the Valsartan manufacturing process to reduce the current conversion rate (60% - 70%) of the known isomer impurity D-Valsartan in the final API and increase batch yields (current batch yield 400 - 500 Kg per batch).

i) you did not conduct and document a formal risk assessment for Change Request PCRC-11025 to evaluate the potential impact of proposed changes on the quality of the intermediates or the final API for this critical change to your validated manufacturing process prior to your quality unit approving the change.

ii) you hired an outside laboratory to conduct a small lab scale research project. Based on the results of a lab scale research project you initiated validation on a commercial scale to change your validated manufacturing process without conducting pilot scale or other small scale batches. Your Deputy Director of Manufacturing stated you have commercial experience and since you only changed the catalyst and the solvent there was no need to conduct pilot scale trial batches before instituting critical changes on a commercial scale.

You initiated validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to your validated manufacturing process on the quality of intermediates and APIs. You do not have a quality agreement with the outside laboratory you used to perform a lab scale research project requiring (prior to initiating testing and reporting results): qualification of all instruments used to conduct tests; validation of all software used with qualified instruments to conduct tests; calibration of all applicable measurement devices against traceable standards prior to use; use of official standards as appropriate; if applicable, establishing system suitability prior to testing samples and processing data; and validation of all test methods used for testing.

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	Cheryl Clausen	Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

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b) you do not have an adequate change control system requiring scientific judgement to determine what additional testing and validation studies are appropriate to justify changes to a validated manufacturing process. You do not always have data to support approval of changes to validated processes.

i) You did not identify specific parameters and specify acceptance criteria for those parameters prior to implementing changes, as part of critical Change Request PCRC-11025, to use to evaluate if the implemented changes decreased the isomer conversion of D-Valsartan and increased the batch yield.

ii) Additional testing requirements associated with critical changes are not always based on sound scientific judgement. Change Request PCRC-11025 included changing both the catalyst and the solvent in your validated manufacturing process. Additional testing requirements associated with these changes were limited to three validation batches and a commitment to conduct additional testing on three batches a year.

c) you do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process. You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change.

d) written change control procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit. Your quality unit does not always follow your written procedure for change control. Your written procedure Change Control System SMP-018.05 effective December 30, 2017 section 5.3.6 (3) specifies QA shall reject the change if the action cannot meet predetermined expectations. Critical Change Request PCRC-11025 did not include acceptance criteria with predetermined expectations. Valsartan Product Development Report-01 dated April 13, 2012 Table 8 includes D-Valsartan isomer impurity (specification < 1.0%) from three batches manufactured according to the validated manufacturing process (results range from 0.46% - 0.57%) and Table 10 includes D-Valsartan isomer impurity from the three

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validation batches manufactured using a different catalyst and solvent (results range from 0.38% - 0.40%). The product development report is silent regarding evaluation of the ability of the implemented changes to reduce isomer conversion rates. Valsartan Product Development Report-01 did not compare the batch weights from batches manufactured immediately before the change to the validated manufacturing process and the first batches manufactured after implementing changes to the manufacturing process.

OBSERVATION 2
Validation of production processes, cleaning procedures, analytical methods, and in-process control test procedures are not always adequate. Specifically,
a) your manufacturing processes are not always capable of consistently producing final products meeting all product quality specifications. Deviation No. DCB18-17017 was initiated for OOS genotoxic impurity Ethyl Carbamate 0.29 ppm (specification < 0.24 ppm) in Levetiracetam batch C5152-17-289M. Repeat test results included OOS results. As a corrective action you reprocessed Levetiracetam batch C5152-17-289M by repeating the final purification step in your manufacturing process. You did not investigate corrective actions to your manufacturing process or to the manufacturing batch record to improve product consistency and manufacturing reproducibility, and to reduce the level of Ethyl Carbamate in the Levetiracetam intermediate crude. You did not develop a prevent action plan to prevent future OOS Ethyl Carbamate levels in the intermediate crude and final API.

Between December 16, 2016 and August 22, 2017 you initiated 17 OOS investigations for Ethyl Carbamate impurity in Levetiracetam. Of the 17 OOS investigations initiated for Ethyl Carbamate impurity in Levetiracetam you attributed 13 OOS results to lab related errors, 5 OOS results to production errors, and 2 OOS results to a combination of lab and production errors. You reprocessed all 17 Levetiracetam batches you investigated for OOS Ethyl Carbamate impurity.

b) written validation protocols are not always adequate.
i) Your Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 and Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) do not include the specific parameters with acceptance criteria to establish your manufacturing process is not only consistent and reproducible but able to fulfill the purpose for changing your validated manufacturing process.
ii) Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor

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Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) specified the number of manufacturing batches to be manufactured as part of validation of your manufacturing process or discussed the number of validation batches to manufacture based on the complexity of the process or the magnitude of the process change.

iii) Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) included a sampling plan designed to demonstrate the consistency and reproducibility of your manufacturing process through batch uniformity data.

c) you do not always initiate investigations during process validation. Tadalafil process validation batch D2182-16-003 test results for Diastereo-isomer 2.22% (specification < 3.0%) were OOT (Out-of-Trend) compared to the other five validation batches with Diasterio-isomer results ranging from 0.20% to 0.57%. You did not initiate an investigation to identify the CPP(s) (Critical Process Parameter), non-critical process parameter(s), raw material(s), or other influences which could impact Diastereo-isomer results in an effort to improve the quality and consistency of TD-2 (the product from the second synthesis step in the manufacture of Tadalafil).

d) you do not have sufficient data to demonstrate your in-house test methods, used for Assay and Related Substance testing of Valsartan, are at least equivalent to USP Monograph test methods. Valsartan USP Method and In-house Method Qualification Comparison Research Report VLDor-10-099 (R) version 2 effective August 29, 2014 does not include data showing you tested known concentrations of Valsartan and spiked Valsartan samples and then compared the results from your in-house test method with results from tested known concentrations of Valsartan and spiked Valsartan samples using the USP method to verify your in-house test results at least meet the acceptance criteria of the USP methods.

e) you do not have validated cleaning procedures. Cleaning procedures for reactors W02-203-1 and W02-204-3 in workshop W02, used in the manufacture of crude Valsartan, are not validated in that you do not have data to demonstrate the cleaning procedure is effective following manufacture of 100 consecutive batches. The most recent cleaning validation study, CVD-18015 (R), approved in July 2018, is based on 60 consecutive batches. The 2016 equipment use log for reactor W02-203-1 shows 97 consecutive batches were manufactured before cleaning. The 2016 equipment use log for reactor W02-204-3 shows 98 consecutive batches were manufactured before cleaning. Your Quality Assurance Director verbally confirmed no rinse samples were analyzed following either of these cleanings.

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OBSERVATION 3

The system for managing quality to ensure confidence that the API will meet its intended specifications for quality and purity is not adequate in that your quality unit lacks written procedures and the authority and responsibility to ensure all critical deviations are thoroughly investigated. Specifically,

a) you release finished APIs manufactured from crude intermediates with OOS levels of genotoxic impurities without conducting a thorough investigation. Deviation No. DCB18-17025 initiated December 13, 2017 and closed April 16, 2018 was initiated for OOS Ethyl Carbamate impurity 0.32 ppm (specification < 0.24 ppm) in Levetiracetam batch C5152-17-432. You identified the root cause as an equipment failure which impacted intermediate crude Levetiracetam batch C2447-17-411 during distillation. You reprocessed Levetiracetam batch C5152-17-432. Intermediate crude Levetiracetam batch C2447-17-411 was also used in Levetiracetam API final batch C5152-17-433. You did not reprocess batch C5152-17-433 made from OOS intermediate crude Levetiracetam batch C2447-17-411. You did not open an investigation, or conduct additional testing on batch C5152-17-433. Your QA Director stated batch C5152-17-433 met the product release specification for Related Substance Ethyl Carbamate.

b) major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 and D5191-17-024 with OOS results for a single unknown impurity (specification < 0.10%). You confirmed OOS results for Valsartan batches D5191-17-023 single unknown impurity 0.33%, and D5191-17-024 single unknown impurity 0.38%.

i) you did not identify a root cause for the single unknown impurity results in batches D5191-17-023 and D5191-17-024. You stated the root cause was probably due to occasional fluctuation in your manufacturing process. You did not attempt to identify this single unknown impurity. You did not attempt to identify the source of fluctuations in your manufacturing process for Valsartan.

ii) you did not develop an adequate Corrective Action and Preventive Action (CAPA) plan. The CAPA you listed on Deviation Investigation Report Form for Deviation DDW02-17003 included: discarding both batches, and following-up on the next 30 batches to see if a similar issue occurs. You did not review your manufacturing process and manufacturing batch records to determine if your manufacturing process and manufacturing batch records could be revised to reduce process variation. You did not interview employees to determine if employees consistently and reproducibly follow your manufacturing instructions.

iii) you did not conduct a thorough risk assessment. Your risk assessment consisted of answering 26 generic

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questions: yes, no, or NA (Not Applicable). Deviation DDW02-17003 investigation did not include documentation showing a more thorough risk assessment was conducted by your risk management team. Your written procedure for Quality Risk Management SMP-023.03 effective November 1, 2017 section 7.1.3 specifies a risk management team should be established when solving major risk issues, and section 7.1.5 of the same procedure specifies to select different tools according to the risk category. Quality Risk Management SMP-023.03 section 8.3 specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not specify which risk management methods and tools to use in association with specific deviation categories.

c) you do not always thoroughly document investigations. your written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018 section 6.4.2 specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP-17.04 effective May 30, 2016). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

d) you do not always thoroughly investigate deviations before closing the deviation. Deviation DCB02-17002 was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification <0.50%) Valsartan intermediate condensate HCl batches C20213-17-339 (0.56%) and C20214-17-340 (0.56%). The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) 3.2 minutes is an in-process impurity observed in other batches but at levels not more than 0.10%. You did not identify a root cause. Your corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity. You did not develop a preventive action plan. You did not identify the single unknown impurity. You reprocessed Valsartan intermediate condensate HCl batches C20213-17-339 and C20214-17-340 and assigned the reprocessed batches final API batch numbers C5355-18-023M and C5355-17-024M. You then closed the investigation without identifying the single unknown impurity.

e) you do not always follow your written procedures. Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature. You classified Return No. RC-18006 as not quality related for Valsartan batches C5069-15-034MM and C5069-15-037MMM returned for not complying with customer PSD specifications, a

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physical feature. The Treatment Record section and closure date on Return No. RC-18006 were left blank.

OBSERVATION 4

The quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs. Specifically, Valsartan batch C5069-15-037M (M designates the batch was micronized) did not meet your customer's specification for PSD (Particle Size Distribution D (0.9) 50 – 85 µm). The actual PSD values were not reported on the CoA (Certificate Analysis for the batch. The quality unit did not complete a Product Release Form rejecting the batch for not meeting the customer's PSD specification with instructions for handling the batch.

Valsartan batch C5069-15-037M was micronized a second time and the batch number was changed to batch C5069-15-037MM (D (0.9) 84 µm). The quality unit completed a Product Release Form and identified the batch as released without further instructions for handling the batch. Yet Valsartan batch C5069-15-037MM was micronized a third time. After Valsartan batch C5069-15-037MM was micronized a third time PSD results were D (0.9) 71 µm. The quality unit completed a Product Release Form releasing the batch a second time.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 5

Cleaning procedures do not contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Specifically, your cleaning procedures are inadequate in that three of the three reactors examined during the inspection contained visible residue or apparent foreign material. Reactor W02-102-1 contained apparent white particulate matter and what appeared to be a red-colored metallic particle. Reactor W02-102-2 contained apparent white residue. Reactor II-250 also contained apparent white residue along the length of the agitator shaft.

OBSERVATION 6

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, and maintenance. This is a repeat observation. Specifically, a) you do not maintain equipment in a good state of repair. The end of the agitator shaft in reactor II-250 is not adequately repaired. The repaired area on the agitator shaft consists of three different colored unidentified materials: yellow, dull gray, and a silver metallic. Your Engineering Supervisor stated the dull gray material is the base layer of a liner repair material and the metallic-appearing material is the top layer of the same repair material.

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Only a small portion of the base layer covered the repaired area. The durability of the base layer in the absence of the top layer is unknown. The yellow material is unknown.

b) you do not have adequate lighting in glass lined reactors to inspect reactors after cleaning to ensure no visible residue remains.

c) you do not have an adequate heat sealing machine to seal final API aluminum bags. Heat sealing machine W05-811 does not have sufficient controls for pressure and time to ensure proper sealing. You do not conduct leak tests to check bag seals prior to final product approval and release.

OBSERVATION 7
Schedules and procedures for preventive maintenance of equipment are not adequate or do not exist. Specifically,

a) you do not have a written procedure describing how to conduct a spark test to verify the integrity of the interior surface of the glass-lined reactors in your manufacturing workshops. Glass-lined reactors are used in the manufacture of crude Valsartan in workshops 2, 13, and W02.

b) you do not have a written procedure describing how to perform repairs to the interior surfaces of glass-lined reactors. Repairs to interior surfaces of glass-lined reactors are made by your employees without written instructions for how to make those repairs.

c) you do not have a record showing a spark test was performed immediately following a repair to the glass-lining of the agitator shaft in reactor II-250. Reactor II-250 is used in the manufacture of crude Valsartan.

OBSERVATION 8
Substances associated with the operation of equipment, such as lubricants, heating fluids or coolants are not always food grade lubricants and oils. Specifically, you use Ethylene Glycol in all of your jacketed glass-lined reactors in Workshop 5. You do not test Ethylene Glycol prior to release for use for Diethylene Glycol, a potential toxic contaminant. Rather than preventing potential finished API contamination from Diethylene Glycol by testing Ethylene Glycol for Diethylene Glycol prior to approval and release, your QA Director stated you periodically monitor your finished product APIs for Diethylene Glycol contamination.

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LABORATORY SYSTEM
OBSERVATION 9
Sampling plans, and test procedures are not always scientifically sound and appropriate to ensure raw materials, intermediates and APIs conform to established standards of quality.
a) you do not always have scientifically sound reasons for invalidating OOS results for lab related reasons. This is a repeat observation. Complaint No. CC-16008 received September 13, 2016 for Levetiracetam batches C5152-16-243 (0.25 ppm Ethyl Carbamate impurity) and C5152-16-254 (0.68 ppm Ethyl Carbamate impurity) failing to meet Ethyl Carbamate impurity specification < 0.24 ppm identifies the complaint as a quality complaint for product quality attribute. Your Vice President of Analytical Operations stated a Single Quadrupole LC-MS is not as sensitive as a Triple Quadrupole LC-MS and sometimes it gives false positive results. Your customer tested Levetiracetam batches C5152-16-243 and C5152-16-254 using a Triple Quadrupole LC-MS. You sent samples of C5152-16-243 and C5152-16-254 to an outside laboratory to test using a Triple Quadrupole LC-MS. Your customer provided you with their LC-MS test method. The outside laboratory used a Triple Quadrupole LC-MS but did not follow the test method provided by your customer.

You do not have a quality agreement with this outside laboratory requiring all equipment used for testing is qualified, any software used with the instrument is validated, and the test method used is validated prior to reporting results. You used results from this outside laboratory for Levetiracetam batches C5152-16-243 and C5152-16-254 to invalidate the OOS results reported by your customer. After your customer returned Levetiracetam batches C5152-16-243 and C5152-16-254 you reprocessed the batches and assigned the reprocessed batches new batch numbers C5152-16-243R and C5152-16-254R. Finished API batches C5152-16-243R and C5152-16-254R were then sold to other customers.

b) you do not have scientifically sound sampling plans.
i) Sampling Procedure for API Raw Material QC-026-9 effective September 30, 2017 includes sampling instructions designed to obscure non-homogenous raw material batches. As an example, section 5.6 specifies to sample the top, middle and bottom of each compartment in the tanker and composite the compartment sample and then composite the composite samples from all the compartments. You do not have data establishing inter-batch and intra-batch homogeneity for key starting materials.
ii) Sampling procedures lack sufficient details describing how to collect samples to ensure the sampling

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		Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

procedure is consistently and reproducibly followed. Sampling Procedure for APIs QA-005-5 effective August 30, 2017 is silent regarding which drums to sample or how to collect samples from the sampled drums.

c) you do not have data to support reduced testing for genotoxic and other impurities. During process validation for Valsartan you committed to testing the final API validation batches for elemental impurities and residual solvents, DMF and MTBE. After the three Valsartan validation batches you test three batches each year for elemental impurities and residual solvents. During process validation for Tadalafil you tested the finished API validation batches for potential genotoxic impurity methyl chloroacetate. After the validation batches you test three batches each year for potential genotoxic impurity methyl chloroacetate.

OBSERVATION 10

Your on-going testing program to monitor the stability characteristics of APIs to confirm appropriate storage conditions and retest dates is not adequate. Specifically,

a) you subjected Valsartan API samples to conditions expected to cause degradation (forced degradation). You did not conduct full product release testing on those forced degradation samples, using validated test methods, to identify the specific product release test(s) that are stability indicating. Instead you included forced degradation samples in three HPLC test method validations for Related Substance, Assay and D-Valsartan impurity. Not all potential product degradants can be identified by HPLC test methods. Product release tests for Valsartan include tests for identification of Residual Solvents by GC-FID. You did not test forced degradation samples for Residual Solvents by GC-FID.

b) you do not always appropriately add stability study samples to your stability study program. Deviation investigation DCB02-17002 was initiated for Valsartan intermediate condensate HCl batches C20213-17-339 single unknown impurity 0.56% (specification < 0.5%) and C20213-17-340 single unknown impurity 0.56%. You reprocessed the batches. You assigned the following batch numbers to the finished APIs made from the aforementioned Valsartan intermediate condensate HCl batches: C5355-18-024 and C5355-18-023. You did not add batches C5355-18-024 and C5355-18-023 to your stability study program.

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PRODUCTION SYSTEM

OBSERVATION 11

Production deviations are not always reported and evaluated and critical deviations are not always investigated and the conclusions recorded. Specifically,

a) your production operators do not always follow batch production instructions for critical processing parameters. At approximately 16:48 on July 24, 2018, the temperature monitor for Reactor II-201 used in the manufacture of Valsartan crude HCl condensate batch C20213-18-291 displayed 64.5 degrees C. The manufacturing batch record for Valsartan crude HCl condensate showed the manufacturing process for intermediate Valsartan from chemical synthesis second step was at step 5.6 in the manufacturing process. The batch record identifies the parameters for this step as 65℃ -70℃ maintained for 5 + 1 hour. The batch record also identifies this 5 + 1 hour time duration as critical. The previous batch record entry recorded at 16:40 lists a temperature of 69.5℃. The temperature for step 5.6 is controlled by a manual steam valve.

b) on July 25, 2018 in workshop 13, a production employee was observed recording a value of 2200 liters for the amount of salt water added at step 7.7 in the batch manufacturing record during the production of crude Valsartan batch C20329-18-261. The flowmeter for the salt water displayed a value of 1.89. A production operator in Workshop 13 stated 1.89 equates to 1,890 liters. The specification for salt water at step 7.7 in the batch manufacturing record for crude Valsartan is 2200 +/- 200L.

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